

ARBEIT UNTER DER LEITUNG VON PROF. DR. MED. ROBERT WENNER
A. O. PROFESSOR AN DER UNIVERSITÄT BASEL

Observations on Three Diabetic Pregnancies

Inaugural-Dissertation
zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt von
Norman Burg
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OBSERVATIONS ON THREE DIABETIC PREGNANCIES

Introduction

The problem of the pregnant diabetic is one that has become common only in the last three decades. Prior to the discovery of insulin, sterility was high among diabetics (1), and the combination of diabetes and pregnancy was relatively rare. When a diabetic succeeded in becoming pregnant in the preinsulin era, a fetal and maternal mortality, both ranging from 30-50 % (1,2,3,4) was to be contended with. The relative sterility of these preinsulin diabetics could be partly attributed to the nutritional deficiencies associated with uncontrolled diabetes (3), amenorrhea, dysmenorrhea, chronic endometritis and vulvitis (5), and early climacterium, all of which frequently accompanied diabetes.

With the introduction of insulin, the relative infertility of the diabetics disappeared and the maternal mortality decreased to 0,6% (3). The fetal mortality however, remained at its preinsulin level (7). The problem arising from the now frequent combination of diabetes and pregnancy is solely one of reducing this high fetal and neonatal mortality.

In the following paper three diabetic pregnancies will be reported and discussed.

Pregnancy I and II

A 30 year old nullipara with no history of diabetes in the family. The patient reports always being well, no weight loss, and never any polyuria or polydipsia. In December 1951 the first pregnancy was established. The examining physician reports the patient in excellent physical condition. The routine urines for the first five months of pregnancy were always negative. Blood pressure varied around 115/85. No edema or weight gain beyond the physiological range was noted. There was never any hyperemesis. The patient left the country around the 22nd week of pregnancy and could not be observed until her return six weeks later. At that time she showed a slight weight loss and complained of persistent

thirst and malaise. On the second day following her return, her condition became acute. Her personal physician, called on emergency, found the patient unconscious, exhibiting Kussmaul respiration, and a breath that smelled strongly of acetone. She was immediately hospitalized with a diagnosis diabetic coma, pregnancy 28 weeks. The blood sugar was then 975 mg%. A section was performed on the unconscious patient, and a dead, immature fetus was removed. In the next six hours, doses of 80 and 100 units of insulin were given hourly, until a total of 540 units had been administered. Six hours postoperatively the blood sugar was 650 mg%, and twelve hours later it was 130 mg%. The further postoperative course was without complication. After the eleventh postoperative day no more insulin was given. The patient recovered rapidly and showed no diabetic symptoms. The blood sugar remained below 120 mg%, urines were always negative. Twenty days after the operation the patient was discharged asymptomatic and in good condition.

No symptoms of manifest diabetes were noted in the twelve month period thereafter. The prospect of future pregnancy was strongly discouraged by the physician. Despite this advice, this patient became pregnant again the following year. She remained under medical supervision during the entire pregnancy. The first five months showed a normal blood sugar, a slight glycosuria but an otherwise normal urine. Around the 30th week a sudden rise in blood sugar (212 mg%) was noted, accompanied by an increased glycosuria, and the appearance of acetone. Nausea and vomiting also appeared for the first time. The patient was hospitalized and the following course was observed:

During the 37th week a caesarian section was performed. A living apparently healthy child, weighing 3300 gms. was delivered. A large hydramnion was observed and a manual removal of the placenta was necessary. Following the section a persistent glycosuria was noted and a blood sugar that varied around 200 mg%.

The baby born was cyanotic when delivered, but improved immediately and cried loudly. There was an extensive collar-edema around the neck and upper thorax. The arms and legs were likewise edematous, but considerably less so. No malformations were noted. At birth the blood sugar was 80 mg%, three hours later it was 57 mg%, at which point 40 cc. of 10% glucose was given per os. In the following hours the baby began displaying signs of respiratory distress. Oxygen and respiratory stimulants were administered. Respiration was rapid and irregular. Râles were audible throughout both lungs. X-Ray revealed a heart enlarged in all directions, extensive atelectases of the right upper lung, and a diffuse clouding of the remaining lung areas, indicative of poor respiratory function. Nine hours postpartum the blood sugar was 91 mg%, the child was extremely dyspneic, cyanotic, and in a state of collapse. The skin was marmorized. 0.3 cc. of 1% adrenalin was given. The cyanosis became generalized and blue grey in color. Respiration became poorer in the next hour, the cyanosis spotty, especially of the extremities. Breathing came in gasps, exitus eleven hours postpartum.

Autopsy report:

Diagnosis: Minimal expansion of the lungs with many hyaline membranes. Slight aspiration of blood. Cyanosis of the internal organs. Extensive dilation of the heart. No significant anomalies. Diffuse fatty degeneration of the liver with erythropoietic centers.

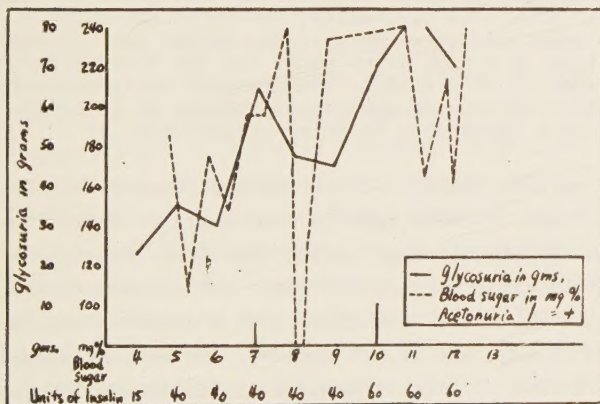
Histopathological examination of the lungs: Very well developed hyaline membranes that are often very thick and almost completely filled the alveoli. A few erythrocytes are occasionally found in the alveoli.

Pregnancy III

A 28 year old nullipara reports a family history negative for diabetes. In the winter of 1951 the patient developed a diabetes that was adequately controlled with 8 units of PZI daily and a diet of 155 grams of carbohydrates.

In the summer of 1953 the first pregnancy was established. During the first six months the insulin requirement rose sharply, so that by the 25th week 55 units of insulin were required daily. The patient never displayed any other complications, with the exception of an occasional episode of hypoglycemia. At the 27th week the patient was hospitalized for a reevaluation of the diabetes and insulin need. The patient was comfortable and in good general condition. The blood pressure was 135/80. The brief hospital stay is recorded below:

TAB. II



GLYCOSURIA, BLOOD SUGAR, ACETONURIA, INSULIN CONSUMPTION 27th WK. PREG. III

It was decided that a diet of 200 grams of carbohydrate and two daily dosages of 35 and 30 units of NPH insulin would be sufficient to keep the blood sugar below 180 mg%. The values for estradiol were 250 μ /24h and estriol 500 μ /24h, during the 29th week. At the 36th week a breech presentation was diagnosed. Four days later the heart sounds were no longer heard and movement no longer felt. X-Ray confirmed the death of the fetus. During the 41st week induction was attempted without success. At the end of the 42nd week a large child (3130 gms.) was manually extracted with much difficulty. The patient developed pyelitis postpartum and the blood sugar remained markedly unstable.

Discussion

In the first pregnancy, the crucial period was between the 22nd and the 28th weeks, the period when the patient was not under medical observation. The development of an almost classical case of acute diabetes gravidarum is witnessed here. This form of diabetes has been described by Gerstmann and Klatfen as follows:

No history of diabetes in the family. A young gravida, with possibly several previous pregnancies that resulted in miscarriages, premature deliveries, or overweight infants. The diabetes makes its appearance in the second half of the pregnancy; there is a high urine sugar but the blood sugar need not necessarily be elevated. Both respond to insulin. Post partum the condition disappears as acutely as it arose. There tends to be a recurrence in later pregnancies (4).

The patient's personal physician who watched progress of the pregnancy for the first 22 weeks, reports absolutely no deviation from the norm of any of the findings during that time. Faced by the same patient six weeks later in diabetic coma, one becomes readily impressed with the acuteness with which such a diabetes may develop and the course it may take if not checked. The ensuing operation was mainly performed in view of maternal indications. The rapid disappearance of all diabetic symptoms immediately following removal of the fetus is somewhat suggestive of toxemia. Here the main factor in fetal loss was an uncontrolled diabetes, one that was probably precipitated by the pregnancy and in turn exacerbated by it. Though it has frequently been observed that severe diabetes and even coma are

not incompatible with the delivery of a living child (2,13,21,27) and do not serve as sufficient indication for interruption (2,17), the degree to which the situation here had deteriorated made immediate operation imperative (5,12,19,32). Had the patient been under constant supervision, the outcome probably would have been more successful. In an individual possessing a marginally functioning pancreas, the affect of a pregnancy may literally push the entire carbohydrate metabolism "over the edge" and result in an acute onset of diabetes. With the removal of the extra load the pancreas, if not too severely damaged, will recover, as was the fact in the described case.

In the second pregnancy of this patient, the course in the beginning is without acute complication. As soon as symptoms made their appearance a strict therapeutic regime was instituted. The blood sugar was never particularly high and probably of no importance. Given, Douglas and Tolstoi disregard the high blood sugar level as long as the patient is maintaining or gaining weight, shows no symptoms, and has no ketonuria. They maintain that a high blood sugar in no way affects the size of the fetus, fetal mortality, toxemia or ketosis. Their studies support this (14). Despite all efforts here however, the urine was never acetone free. This reflects the extreme degree of metabolic disturbance and is always a bad prognostic sign. Ketoacidosis is a common complication of diabetic pregnancy (16%) (14). It is principally caused by poor control of the diabetes, repeated vomiting, low carbohydrate intake when a high demand exists, and insulin insufficiency (14,8). Substantial loss of antiketogenic material in the form of glucose via the kidneys, together with the higher basal metabolism of pregnancy are predisposing factors (8). Ketoacidosis contributes heavily to fetal mortality and even neonatal death, and is probably responsible in this case for the fatal outcome. Delivery here was by section in the 37th week. The proper selection of the time and method of terminating the diabetic pregnancy is probably the most important factor in fetal salvage. Spontaneous delivery by the vaginal route should only be considered in young, healthy diabetics, with no medical or obstetrical complications, and a

history of no previous accidents (2). If any complication is present, as ketoacidosis was here, the indication for section was and is clear. The time recommended is the 36th-37th week. If there is a history of previous accident, if there are toxic or hormonal signs, or if the fetus is of excessive size - termination is indicated regardless of week if the fetus is viable (2,3,9,14). Since the majority of the fetuses die after the 35th week, section allows for the selection of time and thereby avoids possible intrauterine death. While the surest method, it brings with it the risks associated with its own higher mortality and prematurity of the fetus. Though often indicated, section should not be a routine procedure (14). A large hydramnion was noted, and it is observed in about 10% (17) of diabetic pregnancies, particularly when uncontrolled (21). A disturbance of the water balance, with possible hormonal basis (adrenal cortex, pituitary), has been made responsible; this disturbance will probably cause edema of the infant as well (2), as was also noted here. The direct cause of the neonatal death in this pregnancy was respiratory embarrassment, due to the presence of the hyaline membrane syndrome. This syndrome has been often observed among premature babies as a cause of death (35). Its etiology is uncertain. Asphyxia and cyanosis from other causes such as inadequate airways, atelectases due to aspiration of amniotic fluid, or intracranial hemorrhage due to birth trauma; can be excluded in this case. The treatment of choice consists of incubation, oxygen with 5 % carbon dioxide, gastric suction (33) bronchial aspiration with postural drainage, respiratory stimulants, digitalis, and antibiotics. Here they were employed without success. The hypoglycemia that was here encountered was treated with direct administration of glucose (2). When so checked it plays no significant part in neonatal death. Cardiomegaly, hepatomegaly, with erythropoietic centers as found here, have often been observed as typical findings in children of diabetic mothers (3). The infant born here weighed 3300 grams and was 51 cm. at the 37th week. Overweight babies such as this one, is probably the most frequent finding in diabetic pregnancies. Percentages vary in the different studies from 30.6 % - 80 % (2,3,9,14,20,21). The etiology of this overweight is undecided. Abnormal fat accumulation, edema, and

splanchnomegaly account for part of it (3). Several theories have been advanced in explanation. A normal production of maternal growth hormone in the presence of a hypersensitive fetus (20), or an excessive production of maternal growth hormone in the presence of a normal fetus (21), may result in large babies. High blood sugar does not affect fetal size (1); prediabetics with normal blood sugar show the same frequency of large infants as do manifest diabetics (14). There seems to be no correlation between large babies and the control of the diabetes, the weight of the mother, or the incidence of toxemia (14). The condition is probably due to some disturbance in the general hormonal regulatory mechanism, related to or manifested as diabetes. Recent studies suggest a hormonal basis for the complications observed in diabetic pregnancy (3,28). An extensive hormonal therapy has been advocated (3,28). As no hormonal determinations were made here, and hormone therapy not employed, the exact rôle of hormonal imbalance cannot be evaluated. Total recovery by the mother from the diabetes was not observed this time.

In the third pregnancy, a case of mild diabetes, severely complicated by pregnancy is observed, as opposed to the first ones where in pregnancies are complicated by diabetes. Diabetes is not only a condition associated with a malfunctioning islet system, but is an index of a general hormone instability. Pregnancy has long been recognized as a "polyglandular syndrome" that taxes the entire hormone balance of the normal female. When a known diabetic becomes pregnant and thereby undergoes the additional strain on her already overtaxed hormone system, the unfavorable effect on both mother and fetus can be understood (11). Recent studies suggest that pregnant diabetics destined to meet with some obstetrical accident or complication, indicate this tendency in advance by a distinct disturbance in known and measurable hormone levels in the blood and urine (27,34). A faulty production of progesterone, a poor production or metabolism of estrogen, high levels of serum chorionic gonadotrophin, are involved and become intermediate contributing factors to the complications of late pregnancy (3,28). The values that estrogen, progesterone, and serum chorionic gonadotrophin show in normal late pregnancy (low serum chorionic gonadotrophin, relatively high estrogen and progeste-

ron) are invariably altered (high serum chorionic gonadotrophin, low estrogen and progesteron) in individuals developing complications (28). Although only two hormone determinations were made here - the estradiol was at the lower level of the norm and the estriol was distinctly lowered - we may assume that a hormone disturbance probably existed in our case. The actual value of a hormone substitution therapy as advocated by White, Smith and others appears to be a matter of opinion. White successfully reduced fetal mortality to 11 % (34) by combining hormone therapy with early delivery. Others claim as good results with early delivery alone (13,14,19,31). Since hormone therapy was not employed here, its affect on the outcome cannot be evaluated. The probable hormonal upset was no doubt a contributing factor in the fetal death, if not the cause. Although the insulin requirement was steadily increasing and the blood sugar was unstable, the fact that the patient showed no symptoms and only rarely acetoneuria - let us assume that the clinical control was adequate, if the chemical control was not. The baby was large (3130 gms.), which fits in the diabetic pattern. Fetal death in utero as seen here, is observed six times more frequently in diabetics than non-diabetics (3), and is not related to the severity of the diabetes (14). It is probably caused by a lethal factor associated with hormonal imbalance, which manifests itself as diabetes (27). The postpartum pyelitis that occurred here is observed in 17 % of diabetic pregnancies (3).

In seeking an overall explanation to account for the many complications presented by diabetes and pregnancy, one finds the conclusions of White, Titus, Joslin, and Hunt very satisfactory:

The accidents of diabetic pregnancy cannot be prevented by adequate control of the diabetes, nor are they caused by faulty management Stillbirth is not related to diabetes or coma, but definitely to preeclamptic toxemia, as well as neonatal death and premature delivery, - all related to an abnormal hormone picture, with supernormal serum prolactin as index thereof. Against the abnormal balance the woman destroys the offending placenta (27).

"Only when the entire genetic and vascular problem of diabetes is solved will our experience be equal to the best in non-diabetic obstetric and pediatric experience" (34).

SUMMARY AND CONCLUSIONS

Three diabetic pregnancies with their complications are presented and discussed. The first pregnancy, a case of diabetes gravidarum, shows an apparently normal gravida who suddenly develops acidosis and coma, requiring immediate section. The overloading of a marginally functioning pancreas is suggested as explanation. The complete disappearance of diabetic symptoms following section is observed. The second pregnancy in the same patient is marked by acetonuria. A large living infant is delivered by section in the 37th week. A large hydramnion is noted. The newborn expired eleven hours postpartum under extreme respiratory distress; hyaline membrane syndrome was discovered on autopsy to be the cause. The effects of acidosis and the value of early section are discussed. A hormonal disturbance as the possible cause of the observed complications, is noted. The third pregnancy shows a mild diabetic whose insulin requirement rises sharply during the first half of the pregnancy, but who displays no symptoms. A lowered estrogen level is determined. Fetal death in utero occurs during the 36th week. The role of hormonal imbalance as a factor in the complications of diabetic pregnancy is discussed. Since no hormone therapy was employed in any of the cases, its evaluation here is not possible.

CONCLUSIONS

1. A stricter control of pregnant diabetics, with special regard to the hormone status, should be instituted routinely.
2. The introduction of hormone therapy where indicated, on a wider scale than heretofore, may prove of value in fetal salvage.
3. The use of early section, if toxic or hormonal signs are present or if the history shows previous accident, may improve the outcome of diabetic pregnancies.

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